IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Berndl et al.	Docket No.:	49860
Application No.:	09/937,313	Examiner:	YOUNG
Filed:	9/24/2001	Art Unit:	1618
Customer No.:	26474	Confirmation No.:	8414

For: Solubilizing aids in powder form for solid pharmaceutical presentation forms

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

REPLY BRIEF UNDER 37 C.F.R. §41.41

Sir:

This is a Reply Brief to the Examiner's Answer of May 28, 2009. Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees, to Deposit Account 14.1437. Please credit any excess fees to such account.

Status of Claims

Claims 10 – 12, 14 – 18, and 20 – 24 are pending. Claims 10 – 12, 14 – 18, and 20 – 24 stand rejected. Claims 10 – 12, 14 – 18, and 20 – 24 are being appealed. Claims 1 – 9, 13, 19, and 25 – 28 are canceled. No claims are objected to, allowed, or confirmed. No claims are subject to an election/restriction requirement. No claims have been withdrawn from consideration.

Grounds of Rejection to be Reviewed on Appeal

I. Claims 10 – 12, 14 – 18, 20 and 22 – 24 stand rejected in view of: 35 U.S.C §103(a), US 4,127,422 to Guzi Jr. et al. (hereinafter, "Guzi"), US 5,858,412 to Staniforth et al. (hereinafter, "Staniforth"), and US 6,086,915 to Zeligs et al. (hereinafter, "Zeligs").

II. Claims 10, 15, 16, 18, 20 and 21 stand rejected in view of: 35 U.S.C §103(a), US 6,066,334 to Kolter et al. (hereinafter, "Kolter"), Staniforth, and Zeligs.

Arguments

I. Claims 10 – 12, 14 – 18, 20, and 22 – 24 are not obvious in view of 35 U.S.C §103(a), Guzi, Staniforth, and Zeligs.

A) At the time the present invention was made, no apparent reason existed to make the Examiner's proposed combination.

The excipient produced by the process of claim 10 includes, from 10 to 50% by weight, based on the total weight of said excipient, of a liquid or semisolid solubilizing surface-active substance, comprising ethoxylated sorbitan fatty acid esters, or the products of the reaction of ethylene oxide with castor oil, hydrogenated castor oil or with 12-hydroxystearic acid.

The Advisory action mailed November 17, 2008, explained a rationale once applied to support the rejection, stating, "[t]he '412 patent [Staniforth] provides the specific surfactant while the '915 patent [Zeligs] provides the specific concentrations of

the instant claims." This rationale appears to have been dropped. Appellants note the rationale was not sound, because the amount of one surfactant used in a first composition would not prompt a skilled artisan to alter the amount of a different surfactant in a second, unrelated composition.

The Examiner's Answer asserts it would have been obvious to incorporate surfactants disclosed in Staniforth into the Guzi pigment composition. The Examiner's Answer primarily alleges that certain words found in applicants claims have been spotted in the Staniforth reference. The Examiner's Answer does not make note of column 5, lines 61 – 63, which indicate that, according to Staniforth, an aqueous slurry, not a solution, is spray dried. The only assertion resembling a technical reason to incorporate the Staniforth surfactants into the Guzi pigment composition is provided on page 5, where the Examiner's Answer states, "[i]t would have been obvious to include the surfactants of the '415 patent [*sic*, the '412 patent] in order to improve the compressibility of the resulting microparticles." This assertion, however, fails to consider the Staniforth invention as a whole. At column 5, lines 4 – 9, Staniforth states, "[i]n view of the above objects and others, the present invention is directed to sustained-release formulations comprising an active ingredient, an augmented microcrystalline cellulose which possesses excellent compressibility whether utilized in a direct compression or wet granulation procedure, and a sustained-release carrier." Please note that microcrystalline cellulose is a mandatory component according to Staniforth. At column 6, lines 19 – 22, Staniforth states, "[w]hen utilized in pharmaceutical applications, microcrystalline cellulose is typically used as a tablet binder/diluent in wet granulation and direct compression formulations in amounts of 3 – 30% of the formulation, or more." No apparent reason existed to utilize large amounts of Staniforth's surfactants without microcrystalline cellulose. Using large amounts of liquid or semisolid surface-active substances typically results in formulations having a waxy consistency, and formulations having a waxy consistency cause processability problems.[1] Indeed, at column 6, lines 8 – 10, Staniforth explains, "[m]icrocrystalline cellulose is water-insoluble, but the material has the ability to draw fluid into a tablet by capillary action." Clearly, the technical results described by Staniforth depend on the properties of

[1] See page 1, line 44 – page 2, line 2 of the specification.

the water-insoluble microcrystalline cellulose and its surface properties.

The Examiner's Answer ignores all of this information regarding a mandatory component of the Staniforth composition and focuses almost entirely on column 11, lines 47 – 53, where Staniforth states, "[w]hen the novel excipient of the invention utilizes an anionic surfactant, it has been found that the resultant excipient product surprisingly provides a compressibility which is substantially improved in preferred embodiments even in comparison to the compressibility of normal 'off-the-shelf' commercially available microcrystalline cellulose used in direct compression techniques." Somehow, the Examiner's Answer leaps to the conclusion that the nonionic surfactants described in Staniforth will improve the compressibility of any composition, regardless of whether that composition comprises microcrystalline cellulose. The Examiner's Answer cites no evidence that the Staniforth surfactants would be expected to improve the compressibility of the Guzi pigment composition. Nor does the Examiner's Answer cite evidence indicating that "improved" compressibility would have been desirable in Guzi's pigment composition. In fact, it is entirely unclear what the Examiner's Answer deems an "improvement" in the compressibility of Guzi's pigment composition would constitute. The evidence of record indicates that using large amounts of Staniforth's surfactants without microcrystalline cellulose would only result in formulations having a waxy consistency that would cause processability problems.[2]

On page 5, the Examiner's Answer cites Example 1 of Zeligs, which describes the ingredients of an absorption enhancing formulation for DIM or other insoluble dietary indoles. At column 16, lines 16 – 26, Example 1 of Zeligs specifies that the formulation includes "[a]bout 5 to about 20 percent by weight of the following alone or in combination: phosphatidyl choline …; dioleoyl phosphatidylcholine; phosphatidylglycerol; dioleoylphosphatidylglycerol; dimyristoylphosphatidylcholine; dipalmitoylphosphatidylcholine; phosphatidylethalolamines; phosphatidylserines; or sphingomyelins; or other sources of phospholipids as those from purified Milk Fat Globule Membrane; glycerolesters; poly glycerol esters; or ethoxylated castor oil." The Examiner's Answer asserts, "[t]he skilled artisan would have been motivated to include the surfactants of the '415 patent [*sic*, '915 patent] in order to improve the stability of the

[2] See page 1, line 44 – page 2, line 2 of the specification.

spray dried particles as well."

The Examiner's Answer fails to consider column 16, lines 34 – 45 of Zeligs, which explains that Zeligs also requires about 20 to 40 wt. % of starch, methylcellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, hydroxypropylethylcellulose, pectin, gum Arabic, gelatin, or other polymeric matrix forming preparation that are soluble in water and suitable for spray drying, as well as about 0.5 to about 35 wt. % of any other flow enhancing excipient from silica, or related salt. Thus, like Staniforth, the results achieved by Zeligs depend on the inclusion of other components. No apparent reason existed at the time the present invention was made to utilize Zeligs surfactants without also using these other components. Furthermore, the Examiner's Answer does not cite any portion of Zeligs to support the assertion that the surfactants mentioned in Zeligs would improve the stability of a water-dispersible pigment composition according to Guzi. Nor does the Examiner's Answer cite evidence indicating what "improvement" would have been desirable. The Examiner's Answer does not even specify what would constitute an improvement in stability in the context of the Guzi pigment composition. Without the other components discussed above, the skilled artisan would have expected the resultant composition to have a waxy consistency that would cause processability problems.[3]

Clearly, the proposed combination is based only on a hindsight reconstruction of the claimed invention, and ignores mandatory components of both Staniforth and Zeligs.

B) Even if the Examiner's proposed combination were made, several claim requirements would NOT be met.

i. Spray-drying a solution

Spray-drying a solution consisting essentially of a surface-active substance and a pharmaceutically acceptable polymer was NOT known in Guzi, Staniforth, and Zeligs. A person skilled in the art could NOT have combined the elements described in Guzi, Staniforth, and Zeligs by known methods with no change in their respective functions to

[3] See page 1, line 44 – page 2, line 2 of the specification.

arrive at the present invention. The present invention yields more than predictable results to one of ordinary skill in the art.

The processes according to independent claims 10 and 22 require spray-drying a solution consisting essentially of from 10 to 50% by weight of a liquid or semisolid solubilizing surface-active substance and a pharmaceutically acceptable polymer, or processing the polymer and the surface-active substance in an extruder to obtain a homogeneous melt and subsequently converting the melt into the free-flowing powder. The Office action does not allege it would have been obvious to process the polymer and the surface-active substance in an extruder to obtain a homogeneous melt and subsequently convert the melt into the free-flowing powder.

Why is it significant and unexpected that according to the present invention a solution consisting essentially of a pharmaceutically acceptable homo- or copolymer of N-vinylpyrrolidone and from 10 to 50% by weight of a liquid or semisolid solubilizing surface active substance can be spray-dried?

The rate of dissolution and the bioavailabilty of polymer/active ingredient mixtures are critical in the pharmaceutical arts.[4] For certain active ingredients large amounts, in excess of 10% by weight, based on the tablet weight, of liquid or semisolid surface-active substances must be employed to solubilize the active ingredient.[5] Using large amounts of these solubilizers results in formulations having a waxy consistency, and formulations having a waxy consistency cause processability problems.[6] According to the present invention, however, a large amount (10 to 50% by weight) of a liquid or semisolid solubilizing surface-active substance is employed, and the processability problems are avoided. Indeed, the present invention allows a solution consisting essentially of a pharmaceutically acceptable polymer and a large amount (10 to 50% by weight) of a liquid or semisolid solubilizing surface-active substance to be spray-dried.

On page 9, the Examiner's Answer acknowledges Staniforth and Zeligs do not disclose spray-drying a solution consisting essentially of a surface-active substance and a pharmaceutically acceptable polymer.

Regarding Guzi, page 8 of the Examiner's Answer states, "it remains the position

[4] See page 1, lines 11 – 36 of the specification.
[5] See page 1, lines 44 – 46 of the specification.
[6] See page 1, line 44 – page 2, line 2 of the specification.

of the Examiner that solution [*sic*] of similar composition is in fact spray dried." Each component of the composition is water dispersible." These allegations not only lack evidentiary support, but also contradict teachings of the cited reference. Guzi spray-dries a dispersion not a solution. No evidence supports the Examiner's allegation that a dispersion is equivalent to a solution in the context of the pertinent technology. No evidence supports the assertion that each component of the Guzi composition is water dispersible – let alone water soluble. In fact, at column 1, lines 18 – 20, Guzi explains, "[i]n the past various methods have been proposed to overcome the difficulties of uniformly incorporating pigments in latex paints." As expressed in column 3, lines 44 – 46, Guzi goes to great lengths simply to disperse the pigment particles, and provides no indication that it would be possible to produce a solution comprising even a small amount of the pigment – let alone the large amounts (from 55 to 80%) of pigment mandated by Guzi. The Examiner's Answer does not propose eliminating Guzi's pigment, because doing so would render the Guzi process unsatisfactory for its intended purpose. In fact, on page 9, the Examiner's Answer states, "a pigment being added to an excipient would only enhance the characteristics of the excipient, since it would be easily identifiable …." The evidence of record, however, indicates that such an excipient would be prepared, if at all, by spray-drying a dispersion not a solution. Appellants respectfully submit the rejection does not establish a *prima facie* case of obviousness, because it relies on allegations, which not only lack evidentiary support, but also contradict the teachings of the cited references. The rejection also fails to consider that it is it significant and unexpected that according to the present invention a solution consisting essentially of a pharmaceutically acceptable polymer and from 10 to 50% by weight of a liquid or semisolid solubilizing surface active substance can be spray-dried.

ii. An excipient for use in a solid pharmaceutical dosage form.

The processes according to independent claims 10 and 22 produce an excipient for use in a solid pharmaceutical dosage form. The Examiner's Answer refuses to construe the preamble of the claims as a limitation, asserting, on page 10, "the intended use of the excipient 'adapted for use in a solid pharmaceutical dosage form' is merely a

future intended use limitation." To the contrary, MPEP §2111.02, citing *Catalina Mktg. Int'l v. Coolsavings.com, Inc.*, 289 F.3d at 808-09, 62 USPQ2d at 1785, explains, "'clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention. Without such reliance, however, a preamble generally is not limiting when the claim body describes a structurally complete invention such that deletion of the preamble phrase does not affect the structure or steps of the claimed invention.' Consequently, 'preamble language merely extolling benefits or features of the claimed invention does not limit the claim scope without clear reliance on those benefits or features as patentably significant.'"

Clearly relying on the preamble, appellants requested review of whether an excipient for use in a solid pharmaceutical dosage form was known in Guzi, Staniforth, and Zeligs; and whether one skilled in the art could have combined the elements described in Guzi, Staniforth, and Zeligs by known methods with no change in their respective functions to arrive at an excipient for use in a solid pharmaceutical dosage form.

The rejection is based on a proposed modification to the Guzi excipient based on Staniforth and Zeligs. As expressed in column 1, lines 49 – 68, Guzi relates to dry, water-dispersible compositions having broad compatibility in latex and other aqueous systems, such as paper coating compositions, disposable nonwovens, melamine-formaldehyde laminates, ink systems and universal colorant systems. Guzi does NOT suggest that its excipient – intended to be used in commercial latex paints – would be useful in a solid pharmaceutical dosage form. The rejection is not based on any evidence that the pigments employed in the Guzi pigment compositions would be suitable for use in a solid pharmaceutical dosage form. On page 10, the Examiner's Answer merely states, "[t]he ingredients are all generally recognized as safe and are used in pharmaceutical dosage forms as seen in the Staniforth and Zeligs patents." First, Appellants respectfully submit this assertion is unsupported. Second, arguing a pigment is suitable for use in a pharmaceutical dosage form, because it is generally recognized as safe in latex paint seems disingenuous. Moreover, the Examiner's Answer does not bother to allege that an excipient comprising 55 to 80% pigment, as required by Guzi,

would be suitable for use in a solid pharmaceutical dosage form. For at least these reasons, a *prima facie* case of obviousness has not been established.

iii. Excipient consisting essentially of a pharmaceutically acceptable polymer and a liquid or semisolid solubilizing surface-active substance.

Appellants respectfully submit high amounts (from 55 to 80 wt %) of solid pigment particles, as required by Guzi, are excluded by the transitional phrase "consisting essentially of," because their presence would affect the basic and novel characteristics of the claimed invention. MPEP §2111.03 states, "[i]f an applicant contends that additional steps or materials in the prior art are excluded by the recitation of 'consisting essentially of,' applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. *In re De Lajarte*, 337 F.2d 870, 143 USPQ 256 (CCPA 1964)."

First, it is a basic and novel characteristic of the present invention that a solution consisting essentially of a pharmaceutically acceptable polymer and from 10 to 50% by weight of a liquid or semisolid solubilizing surface active substance can be spray-dried. As discussed above, Staniforth requires the use of microcrystalline cellulose, which is water-insoluble and has the ability to draw fluid into a tablet by capillary action. Similarly, Zeligs requires the use of other components, such as starch or methylcellulose. Without these components a person having ordinary skill in the art would have expected the resultant composition to have a waxy consistency that would cause processability problems. No reason existed to exclude these components. Even, if it is assumed for the sake of argument that a skilled artisan would have excluded these components, Guzi requires a pigment. Therefore, the proposed modification of Guzi would not involve spray-drying a solution, but spray-drying a dispersion.

Second, it is a basic and novel characteristic of the present invention that the claimed process produces an excipient for use in a solid pharmaceutical dosage form. As discussed above, a skilled artisan had no apparent reason to assume the pigments employed in the Guzi pigment compositions, which were intended primarily for use in commercial latex paints, would be suitable for use in a solid pharmaceutical dosage form.

Appellants respectfully note that the discussion above is predicated on following the proposed combination, which ignores mandatory components of both Staniforth and Zeligs. Including Staniforth's microcrystalline cellulose and/or Zeligs' starch would alter the basic and novel characteristics of the present invention even further.

II. Claims 10, 15, 16, 18, 20 and 21 are not obvious in view of 35 U.S.C §103(a), Kolter, Staniforth, and Zeligs.

A) At the time the present invention was made, no apparent reason existed to make the Examiner's proposed combination.

The comments made with regard to the previous rejection are applicable to this rejection as well. The Office action has pointed to no apparent reason to modify the Kolter reference based on Staniforth and Zeligs, but instead, has merely conducted a hindsight reconstruction of the present invention, while ignoring mandatory components of Staniforth and Zeligs.

B) Even if the Examiner's proposed combination were made, several claim requirements would not be met.

i. Spray-drying a solution consisting essentially of a surface-active substance and a pharmaceutically acceptable polymer was NOT known in Kolter, Staniforth, and Zeligs.

The processes according to independent claims 10 and 22 require spray-drying a solution consisting essentially of a surface-active substance and a pharmaceutically acceptable polymer, or processing the polymer and the surface-active substance in an extruder to obtain a homogeneous melt and subsequently converting the melt into the free-flowing powder. The Office action does not allege that it would have been obvious to process the polymer and the surface-active substance in an extruder to obtain a homogeneous melt and subsequently convert the melt into the free-flowing powder.

The Examiner's Answer acknowledges Staniforth and Zeligs do not disclose spray-drying a solution consisting essentially of a surface-active substance and a pharmaceutically acceptable polymer.

Kolter relates to the use of redispersible polymer powders or polymer granules consisting of polyvinyl acetate and N-vinylpyrrolidone-containing polymers as binders for producing pharmaceutical presentations. At column 2, lines 63 – 67, Kolter explains, the redispersible polymer powders are produced by initial emulsion polymerization of vinyl acetate, then addition of the N-vinylpyrrolidone-containing polymer, with or without other ancillary substances, to the resulting shear-stable and fine-particle dispersion, and spray-drying of the mixture. Thus, Kolter describes spray drying a fine-particle dispersion not a solution. In fact, at column 2, lines 52 – 53, Kolter explains, polyvinyl acetate is insoluble in water.

On page 10, the Examiner's Answer states, "[t]he Kolter patent discloses a mixture comprising a copolymer of N-vinylpyrrolidone and a water soluble surfactant, spray-dried into a free flowing copolymer (example 1)." The Examiner does not even allege that Kolter spray-dries a solution. Instead, the Examiner states "emulsifiers are added to the mixture creating a homogeneous mixture of liquids (col. 3, lin. 30 – 45). This homogeneous mixture of liquids would effectively function identically to the instant claims." No evidence of record supports this assertion. Moreover, since the Examiner does not even allege the proposed combination would involve spray-drying a solution, a *prima facie* case of obviousness has not been established.

ii. A person skilled in the art could NOT have combined the elements described in Kolter, Staniforth, and Zeligs by known methods with no change in their respective functions to arrive at the present invention.

At column 2, lines 52 – 53, Kolter explains, polyvinyl acetate is insoluble in water. The Examiner seems to agree that a person of ordinary skill in the art had no apparent reason to omit polyvinyl acetate from the Kolter dispersion, because doing so would render the Kolter process unsatisfactory for its intended purpose of producing redispersible polymer powders or polymer granules consisting of 10 – 95% by weight of

polyvinyl acetate.

On page 11, the Examiner's Answer states, "[t]he surfactants would have acted to emulsify the insoluble polyvinyl acetate and reduce particle agglomeration effectively forming an easily sprayable solution (col. 3, line. 30 – 45)." This assertion misconstrues column 3, line 30 – 45 of Kolter, which relates to emulsifiers employed primarily to emulsify vinyl acetate in the initial emulsion polymerization of vinyl acetate. Column 3, lines 44 – 46 indicate that the emulsifying ancillary substances can be added before, during and after the polymerization, however, no evidence of record supports the Examiner's assertion that these emulsifiers would result in "an easily sprayable solution." Moreover, by speculating only about the effect the emulsifiers might have on the insoluble polyvinyl acetate, the Examiner also fails to consider the invention as a whole. As discussed above, it is significant and unexpected that according to the present invention a solution consisting essentially of a pharmaceutically acceptable polymer and from 10 to 50% by weight of a liquid or semisolid solubilizing surface active substance can be spray-dried. Again, prior to the present invention, using large amounts of these solubilizers resulted in formulations having a waxy consistency, which caused processability problems.[7]

iii. The present invention yields more than predictable results to one of ordinary skill in the art.

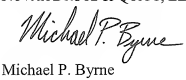
Again, the proposed combination of Kolter, Staniforth, and Zeligs would not have resulted in the present invention. Moreover, as discussed above, the present invention yields results that were not predictable at the time the invention was made. According to the present invention a procedure which permits larger amounts of liquid or semisolid solubilizing surface-active substances to be employed was unexpectedly discovered.

[7] See page 1, line 44 – page 2, line 2 of the specification.

NOVAK DRUCE & QUIGG, LLP
1300 Eye St. N.W.
Suite 1000 West
Washington, D.C. 20005

Phone: (202) 659-0100
Fax: (202) 659-0105

Respectfully submitted,
NOVAK DRUCE & QUIGG, LLP



Michael P. Byrne
Registration No.: 54,015